Remarks

Applicants have carefully considered the Examiner's Action, and respectfully request reconsideration of this Application in view of the foregoing amendments, and the following remarks.

Claims 1-7, 9-11, 20, 27-31 are pending. Claim 1 is amended as shown. The addition of the term "resorbable" is supported at paragraph [0054]. "Sizable" is supported by the ability to cut the resulting preform to shape at paragraph [[0037] and [0042]. "Conductive" is supported by paragraphs [0042] and [0053]. The phrase "interfiber pore size ranges from 0.5 to 10 times fiber diameter providing fluid transport in <10 minutes" is supported at paragraph [0051].

No new matter has been added.

Response to First Rejection under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 1-7, 9-11, 20, and 28-29, and added claim 31, under 35 U.S.C. § 103(a) as being obvious over Shvets *et al., Theor. Exper, Chem.* 37(2):1112-115 (2001) and/or Schacht *et al., Science* 273(8/9):768-771 (1996) and Bellantone *et al.* (US 6,482,444). In making this rejection, the Examiner relies upon Shvets as teaching fiber formation in silica in an acid medium, starting with tetraethyl orthosilicate (TEOS) or tetrabutyl orthosilicate (TBOS), cetyltrimethylammonium bromide (CTMABr) or cetyltrimethylammonium chloride (CTMACl) and HCl. The Examiner relies upon Schacht as teaching silica fibers formed from a material synonymous with TEOS, and suggesting that the "hollow spheres" could be used for drug delivery. However, while the Examiner agrees that neither Shvets nor Schacht teaches the specific limitations of Applicants' claimed invention (see page 4), she argues that since the fibers are formed by what is alleged to be an "almost identical method" and "all of the same ingredients are utilized," that the "properties of the fibrous preform" comprising Applicants claimed invention are also the properties of the Shvets' fibers. Applicants traverse such a conclusion as inaccurate and misleading since Shvets offers no teaching of *hollow* core fibers or of Applicants' *fibrous preform comprising hollow core fibers in a porous network.*

However, recognizing the deficiencies of the cited art, the Examiner points out that both Shvets and Schacht fail to teach a fibrous composite that comprises biodegradable polymers, or a bioactive agent or delivery of a bioactive agent. Thus, the Examiner further cites Bellantone for disclosing a bioactive, biodegradable composite material comprising a fibrous composite of oxides and biodegradable polymers, wherein fibers of the composite comprise oxide materials

with nano-sized pores. Combining Shvets for the process of forming silica fibers, Schacht for suggesting the use of hollow spheres for drug delivery, and Bellantone for using fibrous composites of oxides for controlled release systems, the Examiner has asserted obviousness of Applicants' claimed invention. However, for the reasons discussed below, Applicants traverse the rejection.

There are several significant differences between the materials taught by Shvets and/or Schacht and those of the present invention.

Distinction (1). Applicants' invention is specific to a fibrous preform comprising *hollow* core fibers, see Figure 2, which as indicated at paragraph [0036], "further increase the surface area and lower the density of the composite material." The claims do not include any claim to the method of synthesizing the composition. Instead, the claims are drawn to the composition itself, having hollow core fibers that upon formulation, self assemble into a preform construct. Also claimed are methods for using the construct to deliver a bioactive agent. Applicants' hollow core fiber preform was prepared as shown in FIG 1, and as described in paragraph [0077], wherein "After emulsification, terabutylorthosilicate (TBOS) as silicon source is added dropwise to the solution. The solution is held at room temperature for 5 to 7 days to allow reaction without stirring." This process results in a unique preform that can be shaped or cut to size ("sizable") for implant purposes, and which offers fast transport characteristics ("conductive interconnecting-porous configuration . . . providing fluid transport in <10 minutes), for delivering an active agent therefrom ("wherein (i) nanopores ranging in size from 1.5 to 10 nm in diameter are on the surface of the interconnected fibers; and wherein the resulting fibrous composite has an overall surface area of greater than 1000 m^2/g; (ii) mesopores and macropores are interspaced between and among the interconnecting fibers of the porous configuration, and (iii) interfiber pore size ranges from 0.5 to 10 times fiber diameter").

Shvets uses similar starting materials (fiber formation in silica in an acid medium, starting with tetraethyl orthosilicate (TEOS) or tetrabutyl orthosilicate (TBOS), cetyltrimethylammonium bromide (CTMABr) or cetyltrimethylammonium chloride (CTMACl) and HCl to adjust pH). However, contrary to the Examiner's argument at page 4 of the Action, Shvets' formulation did not, nor would it be expected to, provide a hollow core fiber, fibrous preform. Notably, Shvets' paper reports the careful examination of the resulting constructs by diffractogram analysis (see page 113), yet never once does Shvets report the formation of a

hollow core fiber. Shvets found that the fibers could take the curved form of gyroids, spirals, toroids, helices, or spheres, but in careful structural analysis, all were solid - none were found to be hollow core. Accordingly, Shvets' formulation process differs in some way that is not stated in the paper that prevented the formulation of hollow core fibers. Applicants have found that a substantial amount of TBOS must be added dropwise to form the hollow core fibers. Unfortunately, Shvets offers little information regarding the synthesis process, and instead focuses on the structures that were produced. Therefore, the reference cannot actually be compared with Applicants' invention, except to the extent that it is clear that Shvets was analyzing and characterizing a different final product because Shvets' particles are all *solid*, without a single hollow core fiber or sphere (see shapes depicted in Fig. 1). Given that Shvets' paper describes the thorough structural analysis, including diffractograms and optical microscopy (pg 113; pp 1, line 2) with fiber dimensions from 5 μm (pg 113; pp. 1, line 4) of the resulting particles and forms, it is inconceivable, if hollow core fibers had been produced in Shvets' formulation, that the authors would not have reported such a finding. As a result, while similar starting materials were used by Shvets, the preform assembly process was apparently different from Applicants', thereby producing different products.

Shvets monitored the production process as indicated on the first page of the article (p112), and fibers did not appear until days 5-12. However, as indicated, Shvets' goal was to form a mesoporous molecular sieve, and in the final line of page 115, Shvets defines the process that was used in an acidic media, "which is considerable below the isoelectric point of SiO_2" (see pg 114, pp 3) as "capable of forming *nonporous fibers* and spheres." See page 113, first line of Shvets, referring to the importance of highly acid media ("High acidity favored the formation and growth of fibers in the reaction mixture") but the resulting fibers were still *solid and nonporous*.

In contrast, Applicants' goal is to provide a fibrous preform comprising *hollow core fibers*, which quite simply was not provided by Shvets under the conditions that were defined therein. Thus, the product produced by Shvets under the conditions used in that paper, is a population of solid fiber of various shapes – but which are nonporous and not hollow core - by Shvets' own description. Accordingly, regardless of the similarity of the starting materials, Shvets' disclosure fails to provide or suggest the fibrous preform claimed by Applicants,

"comprising: a plurality of hollow-core fibers assembled into a sizable fibrous preform comprising pores in a conductive interconnecting *porous* configuration."

In the Schacht reference cited by the Examiner, Schacht did not use TBOS, which is an oil. Applicants have found that the oil is important to produce hollow core fibers, presumably, by some micelle transition resulting in hollow core fiber type phase separation, wherein the oil is inside and the shell is water to allow silica precipitation, and other surfactant arrangement into the fibrous geometry. This component is missing from Schacht's formulation.

In contrast to Applicants' invention, Schacht explains, at page 769, middle column, that with stirring, an entirely new material comprises "hollow *spherelike* particles are formed until the fiber morphology disappears completely," and in the third column of page 769, "samples, consisting entirely of such *spherical* particles." Accordingly, Schacht teaches only the formulation of hollow "spheres" – not hollow core fibers. Moreover, any fibers seen by Schacht are solid, with absolutely no reference to a hollow core fiber – and Schacht teaches how to *eliminate any remaining fibers* "to avoid fiber aggregation." Therefore, contrary to Applicants' invention, Schacht's process discloses efforts to remove all fibers from the resulting material. See description of Schacht's brittle hollow spheres at Applicants' paragraph [0016].

Consequently, even if Bellantone were added to the combined Shvets and Schacht references, the resulting composition would still be one of hollow spheres. However, the difference between hollow spheres and hollow core fibers is not simply nomenclature. Schacht's hollow spheres do not communicate with each other, nor could the solid, nonporous fibers produced by Shvets. In marked comparison, the hollow cores of Applicants' fibers are important in that the fibrous preform comprises pores in an "*interconnecting-porous configuration*," (see, express element of claim 1), thereby allowing fluid to rapidly enter and drain. Applicants' fibers may be easily soaked and drained (see paragraph [0050]) providing rapid transport in "10 minutes or less" (see claim 1), unlike many nanocomposites that are difficult to use because the frictional resistance of nano channels to fluid flow is very high. Thus, Applicants' invention, "having a fibrous preform comprising pores in an interconnecting-porous configuration," facilitates substance formation (for example, hydroxyapatite, as Applicants have illustrated in Fig. 5 and 6), and bone growth.

Consequently, contrary to the Examiner's apparent assumption, and regardless of any suggestion in the final paragraph of the paper that using the hollow spheres could *possibly* offer a

"controlled drug delivery system," neither Schacht nor Shvets (nor a combination of the two) mentions, nor implies, any formation of Applicants' hollow core fiber or a plurality of fibers that spontaneously assemble into a fibrous preform comprising pores in an interconnecting-porous configuration.

Distinction (2). As stated by Schacht at page 769, column 3, and as referenced in Applicants' paragraph [0016] Schacht's materials were brittle, and could be crushed with a spatula or even during drying ("most popped open during the drying and calcinations steps"). See caption of Schacht's Fig. 2, and paragraph describing Fig. 2. As Applicants have stated in the application at paragraph [0016], "the brittle nature of the spheres in combination with the fact that they were not porous throughout their interior were unfavorable characteristics for use as a matrix." By comparison, Applicants' bioactive, biodegradable fibrous composite of gel-like oxide materials and biodegradable polymers is ductile and can be easily handled, comprising a plurality of hollow core fibers self-assembled into a fibrous preform comprising pores in an interconnecting-porous configuration. See the reference to the "conductive" embodiment of Applicants' invention at paragraph [0042], as specified in claim 1. The ductile nature of Applicants' invention is partially due to the polymer lips shown in Fig. 4 and mentioned in paragraph [0033].

Thus, the combined prior art offers no teaching or suggestion for how to obtain or form hollow core fibers, let alone how to produce hollow-core fibers having the useful, ductile, and easily handled characteristics of Applicants' invention. Although similar starting material chemistry may be used, important differences were introduced by Applicants over the prior art, as disclosed, to result in the formation of hollow core fiber, fibrous preforms. These differences are at least two-fold. First the materials were selected to provide longer chain precursors, *e.g.*, TBOS rather than TEOS, to result in slower reaction rates. Secondly, Applicants used no organic solvent in the formation of an oil phase. By comparison, in the cited combined prior art precursors, such as TEOS, was dissolved in an organic solvent (for example, mesitylene, see first paragraph of p. 769 of Schacht *et al.*) to constitute an oil phase, which then reacts with the water phase to obtain the final product. In contrast, in Applicants' method, TBOS forms the oil phase itself and no other organic solvent was added (self-assembling into a "fibrous preform").

Distinction (3). Applicants' fibers self-assemble into a fibrous preform having a resorbable, conductive, interconnected-porous configuration, as exemplified at Applicants'

Example 1, which details initial formation of silica fibers within an emulsion comprised of cationic and anionic materials. (See Applicants' Example 1: Method of Preparing and Testing Fibrous Silica Composites.). Applicants' production of a "preform" comprising hollow core fibers (see, express limitation in claim 1) is, therefore, unexpected and non-obvious over the prior art. Applicants' invention requires no post-processing weaving of the fibers into a mat – rather they spontaneously are initially formulated into a "fibrous preform." Moreover, the fibrous preform requires no additional processing steps, such as sintering and/or foam processes to achieve a networked multi-porous fibrous configuration. Consequently, Applicants' claimed invention is entirely different from Shvets or Schacht in any combination, since neither teaches Applicants' "*fibrous preform*" composite.

To fill any gaps in the prior art, the Examiner has further added Bellantone to the cited combined references. Bellantone teaches silver-containing bioactive-glass composites prepared by a sol-gel method. (See, Bellantone col. 2, lines 50-55 and col. 4, lines 30-35.) Thus, the fibers of the Bellantone composite are *not a self-assembled* fibrous *preform*, as required by Applicants' claim 1. Rather, Bellantone's mesh, fabric (woven or non-woven), mats, and three-dimensional structures all require an additional assembly of individual fibers produced by a previous separate step. (See Bellantone, 7, line 8, 17, 20, 23.). For example, in one embodiment, the Bellantone fibers are woven into mats or other structures. (See Bellantone, 7, line 20).

In the prior art, materials either have fast transport (requiring macro or mesopores) or have high surface area (requiring nanopores), but until Applicants' invention, it has never been possible to obtain both by a self assembly process. The prior art teaches that one can achieve a combination of fast transport and high surface area if one uses nanoporous fibers as a starting material, then manually weaving the fibers together into a composite. But such a *post-formulation assembly method* is entirely different from Applicants' spontaneous assembly at the time of formulation to produce the "fibrous preform," wherein "pre" is the key term, meaning formed prior to completion of the formulation – as opposed to by a manual weaving step following formulation ("post formulation"). And in fact, Applicants' method is a significant improvement to the prior art woven methods.

Moreover, while the Examiner cites Bellantone for teaching a fibrous composite having mesopores and macropores, nowhere does Bellantone teach an "*interconnected multi-porous network configuration*" as defined in the invention of Applicants' claim 1. See Applicants'

paragraph [0046]. By comparison, Bellantone, at col. 6, lines 35 -40, describes the post-formation steps that may be taken to adjust the pore volume of the already-formed composite. Thus, any additional pore size or structure in the Bellantone composite, other than nanopores, is necessarily created by a post-formation modification, that requires addition processing, such as sintering and/or foam processes. (See Bellantone, col 6, lines 38-39.) Post processing additions are not an element of Applicants' "fibrous preform."

Consequently, even when the fibers of Bellantone are combined with the brittle, non-interconnected, hollow sphere teaching of Schacht, or the nonporous, solid fibers of Shvets, the combination does not, and cannot, render obvious Applicants' claimed invention. No element provided by the combination offers a *self-assembled* "multi-porous *fibrous* composite *preform*" of Applicants' claimed invention, requiring no post-formation assembly or modification. As a result, since each and every element of the invention of Applicants' claims 1-7, 9-11, 20, 28-29, and 31 is not disclosed, nor even suggested, by the cited combination of references including Bellantone, Applicants respectfully assert that under the law, these claims cannot be shown to be obvious over the cited combination under 35 U.S.C. §103(a). Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn, and that these claims be moved to allowance.

Response to Second Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected claims 27 and 30 under 35 U.S.C. § 103(a) as being obvious over Shvets *et al., Theor. Exper, Chem.* 37(2):1112-115 (2001) and/or Schacht *et al., Science* 273(8/9):768-771 (1996) and Bellantone *et al.* (US 6,482,444), and further in view of Aloha *et al.* (WO 97/45367). In making this rejection, the Examiner relies upon the arguments made regarding the First Rejection under 35 U.S.C. § 103(a), above. However, Applicants ask why the Examiner states at page 10 of the Action, that "Shvets/Schacht/Bellantone teach all of the limitations of claims 20 and 11 upon which claims 27 and 30 depend, but fail to teach the limitations further recited by claims 27 and 30." How is this possible? Claims 27 and 30 narrow the invention. They do not broaden it. Nevertheless, to fill that gap, the Examiner has added Ahola.

Notably, however, the Examiner has made no rejection of claims 20 or 11 in this rejection. Although the Examiner has explained the reasoning behind Ahola's teaching with regard to Applicants' claims 1 and 5, 6 and 11, 7 and 20 and 21, respectively, if the claims

underlying claims 27 and 30 are patentable, for the above-stated reasons, each of which is expressly applied hereto, then claims 27 and 30 must also be patentable, although the converse is not necessarily true. Thus, regarding claims 27 and 30, Applicants traverse the Examiner's conclusion that Applicants' claimed invention is obvious.

With regard to claims 27 and 30, Ahola teaches a dissolvable silica-xerogel prepared via a sol-gel process. More specifically, Ahola teaches a xerogel composite by spray-drying or sol-spinning methods. (See Ahola, page 9, lines 5 – 35.) Thus, the Ahola composite is not, and cannot be, considered to be "self-assembled." Ahola's configurations, specifically, woven or non-woven mats, filters, and fiber-mats, all require additional assembly of silica-xerogel fibers that were previously produced in a separate step. (See Ahola, page 10, line 1, 13, and 16.). Thus, if the prior art composite resulting from Ahola alone or from the cited combined references all require "post-formulation assembly" – they cannot, by definition, be a "fibrous preform." If Ahola is added by the Examiner simply to show the feasibility of adding a drug or therapeutic composition, when the composition is something other than Applicants' fibrous preform composition as it is defined in Applicants' application, then the added reference adds nothing of significance to the combination of Shvets, Schacht and Bellatone which are addressed above. Nothing in Ahola can change the composition to which the drug or therapeutic is added into Applicants' fibrous preform - again with the emphasis on both the fibrous nature of the product and the preform formulation, requiring no post formulation assembly. As a result, such composites requiring post-formulation modification or assembly cannot render obvious Applicants' independent claim 1, nor dependent claims 20 or 29, nor the presently cited claims 27 and 30 in which the "animal is a human."

The cited references in combination cannot teach or suggest more than their various parts. Moreover, as indicated above, while the prior art teaches either fast transport (requiring macro or mesopores) or high surface area (requiring nanopores), the combined prior art has never been able to provide both limitations together. This problem is overcome by Applicants' invention that claims fast transport takes less than 10 minutes, and wherein no "post-formulation" assembly by manual weaving of the fibers is required or claimed. In fact, Applicants' method is a significant improvement to the prior art woven methods.

Moreover, nowhere in the combined cited art is there a teaching of a resorbable, conductive, "*interconnected multi-porous network configuration*" in a self-assembled fibrous

preform, as claimed by Applicants without post-formation modifications that require addition processing, such as sintering and/or foam processes. Consequently, even when the woven fibers of Bellantone are combined with the brittle, non-interconnected, hollow sphere teaching of Schacht, or the nonporous, solid fibers of Shvets, and Ahola's drug or therapeutic composition administration to an animal or human, the combination does not, and cannot, render obvious Applicants' claimed invention. The combination falls to teach every element of Applicants' claimed invention, specifically claim 1, and all claims dependent thereon, including claims 27 and 30, meaning that the cited claims 27 and 30 cannot be obvious over the cited combination under 35 U.S.C. §103(a). Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn, and that these claims be moved to allowance.

Consequently, Applicants respectfully request that under 35 U.S.C. §103(a), all pending claims be reconsidered, whether expressly rejected or not, and moved to allowance. Reconsideration and allowance of the pending claims are respectfully requested at the earliest possible date, and Applicants earnestly solicit a Notice of Allowance. Should the Examiner wish to discuss Applicants' Response, she is asked to please contact Applicants' undersigned representative at the number provided below. If additional fees are due, the Office is authorized to withdraw the necessary amount from Deposit Account 50-4764.

Respectfully submitted,

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